PERGAMON

Phytochemistry 51 (1999) 595–597

PHYTOCHEMISTRY

Two monoterpene alkaloidal derivatives from *Incarvillea sinensis*

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Received 28 April 1998; received in revised form 30 July 1998

Abstract

Two new derivatives of monoterpene alkaloids, named incarvillateine C and incarvillateine D which are related to an antinociceptive alkaloid, incarvillateine, were isolated from the aerial parts of *Incarvillea sinensis* LAM. On the basis of both chemical and spectroscopic evidence, the structures of the first two were characterized as a bis-demethoxy and demethoxy derivatives of incarvillateine, respectively.

Keywords: *Incarvillea sinensis*; Bignoniaceae; Monoterpene; Alkaloid; Incarvillateine

1. Introduction

Incarvillea sinensis LAM has been traditionally used in treating rheumatism and to relieve pain, and this report describes the isolation and characterisation of two monotecpene alkaloids **1** and **2**. We previously reported new alkaloids, such as incarvilline, incarvillateine (**3**) and other monoterpene- or phenyl propanoid-conjugated alkaloidal derivatives from the title plant (Chi et al., 1992; Chi, Hashimoto, Yan, & Nohara, 1995a, 1995b, 1997; Chi, Hashimoto, Yan, Nohara, Yamashita, et al., 1997; Chi, Yan, & Li, 1990). Furthermore, we also found a great potency of antinociception of **3** (Chi, Hashimoto, Nohara, Yan, et al., 1997). To elucidate a correlation between structure and activity, a search for analogous compounds to **3** was undertaken.

2. Results and discussion

The aerial parts of *I. sinensis* were extracted with EtOH, and the extract was subsequently treated with weak acid and alkali, followed by Al_2O_3 and silica gel column chromatography to yield compounds **1** and **2**.

Compound **1**, incarvillateine C, showed a $[M]^+$ ion peak at m/z 658 in its EI–MS. It corresponds to the bis-demethoxy derivative of **3**, as evidenced by both ^1H and ^{13}C NMR spectra. Since two sets of 4-hydroxyphenyl moieties were observed in the ^1H and ^{13}C NMR spectra, the structure of **1** was determined as shown in the formula.

Compound **2**, incarvillateine D showed a $[M+H]^+$ ion peak at m/z 689 in its positive FAB–MS. The ^{13}C NMR signals, except for the aromatic moiety, were consistent with those of **1**. The aromatic carbon signals suggested the presence of a 4-hydroxyphenyl moiety and a 3-methoxy-4-hydroxyphenyl moiety. Since the signals at C–1″ ~ 6″ were in agreement with those of methoxyincarvillateine (Chi, Hashimoto, Yan, & Nohara, 1997), the structure of **2** was established as

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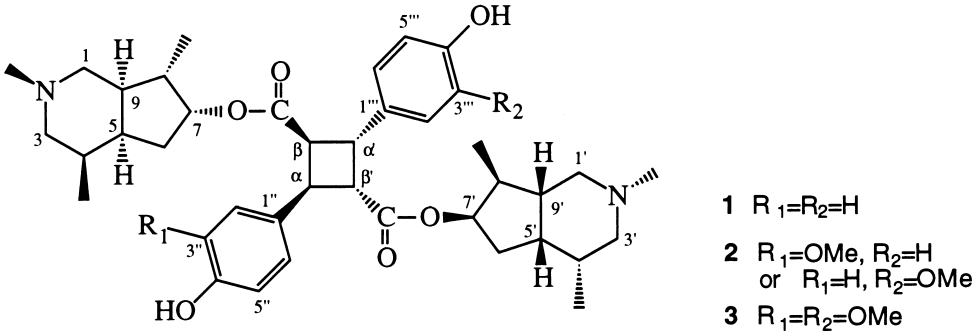
0031-9422/99/$ - see front matter
PII: S0031-9422(99)00003-5



shown. Its structure was also verified by the aid of ^{1}H–^{1}H, ^{1}H–^{13}C COSY and HMBC, and by comparison with **3**, whose structure was previously determined by X-ray analysis (Chi et al., 1990; Chi, Hashimoto, Yan, Nohara, Yamashita, et al., 1997).

3. Experimental

3.1.1. General

^{1}H and ^{13}C NMR: JEOL JNM–GX 500 NMR, int. standard (TMS). The other instruments and reagents used in this study were the same as those described in a preceding paper (Chi et al., 1997).

3.1.2. Extraction and separation

Incarvillea sinensis (Bignoniaceae) was collected in the Hebei province, China, as described in (Chi et al., 1995a). The aerial parts were then exhaustively extracted with EtOH. The EtOH extract was concentrated under reduced pressure to a syrup, which was dissolved in 2% HCl and filtered. The filtrate was adjusted to pH 11 by adding NH_4OH, and the alkaloid was extracted with $CHCl_3$. After removal of solvent *in vacuo* to dryness to give a residue which was repeatedly subjected to Al_2O_3 column chromatography with $CHCl_3$–MeOH–H_2O (10: 1: 0 → 6: 4: 1) as eluant as well as silica gel column chromatography with cyclohexane–MeOH–Et_2NH (30: 1: 1 → 5: 1: 1) to afford compounds **1** (10.1 mg) and **2** (12.5 mg).

3.1.3. Incarvillateine C (*1*)

A white powder, $[\alpha]_D^{17}$–3.2° ($c = 0.30$, $CHCl_3$). EIMS *m/z* (rel. int.): 659 $[M+1]^+$ (2), 658$[M]^+$ (2), 330 (56), 183 (20), 182 (100), 167 (10), 166 (46), 165 (10), 164 (14), 147 (33), 58 (79). ^{1}H–NMR ($CDCl_3$); δ 0.59 (1H, m, 6–H*a*), 0.60 (3H, d, $J = 7.3$ Hz, 8–Me), 0.75 (3H, d, $J = 6.7$ Hz, 4–Me), 0.79 (3H, d, $J = 6.7$ Hz, 4′–Me), 0.83 (3H, d, $J = 7.3$ Hz, 8′–Me), 1.06 (2H, m, 6′–H*a*), 1.54 (4H, m, 1, 1′–H*a*, 3, 3′–H*a*), 1.71 (4H, m, 6, 6′–H*b*, 8, 8′–H), 1.86 (2H, m, 9, 9′–H), 2.03 (2H, m, 4, 4′–H), 2.17 (2H, m, 5, 5′–H), 2.25 (6H, s, *N*, *N*′–Me), 2.54 (2H, m, 3, 3′–H*b*), 2.63 (2H, m, 1, 1′–H*b*), 3.85 (2H, m, β, β′–H), 4.34 (2H, m, α, α′–H), 4.86 (2H, m, 7, 7′–H), 6.72 (4H, d, $J = 8.5$ Hz, 3″, 3‴, 5″, 5‴–H), 7.16 (4H, d, $J = 8.5$ Hz, 2″, 2‴, 6″, 6‴–H). ^{13}C–NMR ($CDCl_3$); Monoterpene moiety: δ 14.6, 14.9 (8, 8′–Me), 17.0, 17.1 (4, 4′–Me), 29.4, 29.9 (C–6, 6′), 30.1, 30.2 (C–4, 4′), 37.3, 37,4 (C–5, 5′), 40.6, 40.7 (C–8, 8′), 46.0 × 2 (*N*, *N*′–Me), 45.6, 45.7 (C–9, 9′), 57.2, 57.3 (C–1, 1′), 57.5, 57.6 (C–3, 3′), 76.5, 76.7 (C–7, 7′); C6–C3 Moieties: 40.9, 41.5 (α, α′–C), 47.2, 48.0 (β, β′–C), 172.3, 172.5 (COO, COO′), 128.8 × 2 (C–2″, 2‴), 115.3 × 2 (C–5″, 5‴), 129.0 × 2 (C–6″, 6‴), 129.9, 130.0 (C–1″, 1‴), 115.4 × 2 (C–3″, 3‴), 156.2, 156.3 (C–4″, 4‴).

3.1.4. Incarvillateine D (*2*)

A white powder, $[\alpha]_D^{16}$–5.1° ($c = 0.30$, $CHCl_3$). Positive FAB–MS *m/z* (rel. int.): 689 $[M+1]^+$ (100), 688$[M]^+$ (29), 687 (48), 361 (12), 360 (48), 359 (11), 331 (24), 330 (96), 328 (15), 307 (29), 289 (24). ^{1}H–NMR ($CDCl_3$); δ 0.58 (1H, m, 6–H*a*), 0.59, 0.80 (each 3H, d, $J = 6.7$, 7.3 Hz, 8, 8′–Me), 0.71, 0.76 (each 3H, d, $J = 6.7$, 7.3 Hz, 4, 4′–Me), 1.06 (1H, m, 6′–H*a*), 1.45 (2H, m, 1, 1′–H*a*), 1.60 (2H, m, 3, 3′–H*a*), 1.71 (2H, m, 6–H*b*, 8–H), 1.85 (4H, m, 6′–H*b*, 8′, 9, 9′–H), 1.95 (3H, m, 4, 4′, 5–H), 2.10 (1H, m, 5′–H), 2.19 (6H, s, *N*, *N*′–Me), 2.47 (2H, m, 3, 3′–H*b*), 2.58 (2H, m, 1, 1′–H*b*), 3.81–3.88 (2H, m, β, β′–H), 3.89 (3H, s, OMe), 4.31–4.37 (2H, m, α, α′–H), 4.89 (2H, m, 7, 7′–H), 6.69 (2H, br d, $J = 8.6$ Hz, 3‴, 5‴–H), 6.80 (3H, m, 2″, 5″, 6″–H), 7.16 (2H, br d, $J = 8.6$ Hz, 2‴, 6‴–H). ^{13}C–NMR ($CDCl_3$). Monoterpene moiety: δ 14.5, 14.9 (8, 8′–Me), 16.9, 17.1 (4, 4′–Me), 29.3, 29.6 (C–6, 6′), 30.1, 30.2 (C–4, 4′), 37.2, 37,3 (C–5, 5′), 40.4, 40.5 (C–8, 8′), 45.9, 46.1 (*N*, *N*′–Me), 45.7, 45.8 (C–9, 9′), 57.1, 57.2 (C–1, 1′), 57.5 × 2 (C–3, 3′), 76.3, 76.4 (C–7, 7′); C6–C3. Moieties: 40.9, 41.9 (α, α′–C), 47.3, 47.8 (β, β′–C), 171.9, 172.1 (COO, COO′), 55.8 (3″–OMe), 110.8, 128.9 (C–2″, 2‴), 114.6, 115.5 (C–5″, 5‴), 120.4, 128.9 (C–6″, 6‴), 129.7, 130.6 (C–1″, 1‴), 145.3, 115.5 (C–3″, 3‴), 146.7, 156.5 (C–4″, 4‴).

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